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PFIZER INC
10555 SCIENCE CENTER DRIVE
SAN DIEGO, CA 92121

EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/775,444	COHEN ET AL.	
	Examiner	Art Unit	
	PARITHOSH K. TUNGATURTHI	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *2,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/08/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1 and 16 in part, 3-13 and 17, drawn to a method of treatment or prevention in a mammal comprising administering to said mammal an amount of a human anti-IGF-IR antibody wherein the disorder is multiple myeloma in the reply filed on 05/24/2007 is acknowledged. The traversal is on the ground(s) that the groups set forth by the Examiner all stem from a common concept and theory, and thus are related and that the prosecution of the claims of Groups I-VIII together would not place a substantially greater burden on the Examiner. This is not found persuasive because restriction requirements are set forth for reasons of patentable distinction between each independent invention so as to warrant separate classification and search. The methods are different because the disorders claimed comprise distinct pathological conditions, including differences in their modes of administration and thus differ in method objectives, method steps and parameters and in the reagents used. The record set forth in the previous restriction requirement clearly indicated that the delineated inventions are in fact patentably distinct each from the other or independent from the other. Further, the different groups require different search terms and different search strategies which create a burden on the examiner. The requirement is still deemed proper and is therefore made FINAL.

2. Claims 2, 14 and 15 are withdrawn from further consideration under 37 C.F.R. 1.142(b) as being drawn to nonelected inventions.

3. Claims 1 and 16 in part, 3-13 and 17, drawn to a method of treatment or prevention in a mammal comprising administering to said mammal an amount of a human anti-IGF-IR antibody wherein the disorder is multiple myeloma are examined to the extent the agent species is “analgesic”, the vaccine species is “autologous tumor vaccines”, the anti-proliferative species is “PDGFR inhibitors”, the antibody species is “2.13.2”, and the VH gene species is "VH DP-47" and the VL gene species is "A30".

4. Please note that the deposit of antibody 2.13.2 is not required, because the specification discloses the amino acid sequences of the light and heavy chains. Please see Figure 3.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 9 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 13 are indefinite for reciting “gene”. According to Genes IV (Lewin et al, Oxford University Press, page 810, 1990), a gene is defined as “the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding regions (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons).” From the teachings of the

specification, however, the nucleic acid sequences introducing antigens or marker elements appear limited to the specific coding regions, and do not include expression control elements that fall under the definition of a gene. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is unclear for reciting "wherein the antibody also comprises CDR regions in its light chain from the A30 gene", because it is not clear if the framework regions of the light chain are obtained from A30 gene or if the CDRs of the light chain are obtained from the A30 gene. Does the applicant mean that the heavy chain CDRs obtained from an anti-IGF-IR antibody and the light chain CDRs obtained from the A30 gene? Appropriate correction is required.

Claim 13 is further unclear for reciting "derived" in line 3, because the term "derived" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of an ascertainable meaning for said phrase. Since it is unclear how the heavy chain amino acid sequence are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derived heavy chain amino acid sequence" are formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for example. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass

proteins with amino acid substitutions, insertions or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 9 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9 and 13 recite “gene”, and hence are broadly drawn to a large genus of nucleic acid molecules and members of the genus are variable because of the potentiality of the many different proteins they may encode. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. Applicants’ disclosure fails to describe any cDNAs that correspond to VH DP-47 and A30, nor is it clear that the resulting sequences would be full-length. The sequence prepared from undefined parts of a cDNA clone may not comprise the entire coding region of any particular gene, nor is it clear that partial

sequences would even be in frame to encode a lung specific gene polypeptide. The claims, as written encompass polynucleotides, which vary substantially in length and also in nucleotide composition. The specification does not contain any disclosure of the function of a full-length open reading frame (ORF) that includes VH DP-47 and A30. For example, the specification does not describe the organization, location or actual DNA sequences of promoter and regulatory regions and introns, all defining elements of a “gene”. The specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

Vas-Cath Inc. v. Mahurkar. 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the ad to recognize that he or she) invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is pad of the invention and reference to a potential method of isolating it. The

compound itself is required. See Fiers v. Revel, 25 USPQZd 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQZd 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQZd 1481 at 1483. In Fiddes, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

9. Claims 1, 3-13 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a disorder in a mammal comprising administering to said mammal a human anti-IGF-IR antibody wherein the disorder is multiple myeloma, wherein the antibody comprises all six CDRs (three from the light chain and three from the heavy chain) of the antibody 2.13.2, **does not reasonably provide enablement** for the method of preventing a disorder in a mammal comprising administering to said mammal an amount of a human anti-IGF-IR antibody wherein the disorder is multiple myeloma OR the method of treatment of prevention of aging in a mammal comprising administering to said mammal an amount of an anti-IGF-IR antibody that is effective in treatment of prevention; wherein the antibody comprises changes within the CDR sequences of antibody 2.13.2 (as in claim 11). The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is cancer prevention where the relative level of skill of those in the art is deemed to be high.

The claims are drawn to a method of preventing a mammal comprising administering to said mammal an amount of a human anti-IGF-IR antibody wherein the disorder is multiple myeloma.

With regards to the prevention of cancer, the specification teaches (Examples 1 and 2, in particular) the effects of antibodies on IGF-IR in vivo and growth inhibition of 3T3/IGF-IR cell tumors. Thus, the specification enables a skilled artisan to treat such tumors associated with IGF-IR. However, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to stimulating immune responses in any and all subjects at risk for developing cancer. This includes the total human population on Earth as all human subjects are at some risk for

developing cancer and applicant have not demonstrated, with any predictability, that the claimed agent(s) would predictably prevent the occurrence of cancer in the human population.

Reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations; some of which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, family histories, or randomized controlled trials. For example, Byers, T. (CA Journal, Vol. 49, No. 6, Nov/Dec. 1999) teaches that randomized controlled trials are commonly regarded as the definitive study for proving causality (1st col., p.358), and that in controlled trials the random assignment of subjects to the intervention eliminates the problems of dietary recalls and controls the effects of both known and unknown confounding factors. Further, Byers suggests that chemo-preventitive trials be designed "long-term" such that testing occurs over many years (2nd col., p. 359). The essential element towards the validation of any preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer. This would require monitoring a large population with the claimed agents and *linking* such results with subsequent histological confirmation of the presence or absence of disease. Furthermore, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of

drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Further, while the specification is enabling for administering anti-IGF-IR antibodies in a subject for treating cancers associated with IGF-IR, the specification does not predictably enable the successful eradication and or prevention of cancer by the administration of anti-IGF-IR antibodies. With reference to treatment or prevention of aging comprising administering anti-IGF-IR antibodies, the specification does not address many complicated issues involved as recognized by the prior art. For example, Yu et al (U.S. Patent 6251863, Date Issued: 06/26/2001) teach that many prominent conditions are associated with aging including lack of mobility and flexibility, osteoporosis, loss of skin elasticity, respiratory distress, muscle loss, memory loss, cognitive and affective impairment, osteodegenerative impairment of the joints, and cardiac failures, etc. In addition to impairment of many body functions associated with normal aging, some people develop advanced forms of these dysfunctions indicating that the method of treating or preventing aging involves the treatment or prevention all such conditions for which the specification does not provide enablement.

Further, claim 11 is drawn to a method of treating multiple myeloma comprising administering antibody comprising changes, such as substitutions, additions or deletions within the heavy and light chain CDR sequences of the antibody 2.13.2.

The specification discloses only IGF-1R antibodies that comprise all six CDRs from the heavy and light chain of 2.13.2. The specification does not teach any IGF-1R antibodies that contain substitutions, additions or deletions with the CDRs. There are no working examples of human antibody variants that bind RG1.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295; IDS-12/08/2004, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, March 1982; IDS-12/08/2004). Rudikoff et al. teach that the alteration of

a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Colman (Research in Immunology, 145:33-36, 1994; IDS-12/08/2004) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). It is unlikely that human antibodies comprising a variable region which does not contain all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their correct spatial orientation have the requisite IGF-1R binding function. Additionally, Bendig M. M. (Methods: A Companion to Methods in Enzymology, 1995; 8:83-93) reviews that the general strategy for "humanizing" antibodies involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see entire document, but especially Figures 1-3). Similarly, the skilled artisan recognized a "chimeric" antibody to be an antibody in which both the heavy chain variable region (which comprises the three heavy chain CDRs) and the light chain variable region (which comprises the three light chain CDRs) of a rodent antibody are recombined with constant region sequences from a human antibody of a desired isotype (see entire document, but especially Figures 1-3). Thus, the state of the art recognized that it would be highly unpredictable that a humanized molecule or antibody comprising an antibody variable region but comprising less than all six CDRs of a parental antibody with a desired specificity would retain the antigen-binding function of the parental antibody. Thus, the minimal structure which the skilled artisan would consider predictive of the function of binding antigen includes six CDRs (three from the

heavy chain variable region and three from the light chain variable region) from the same parental antibody in the context of framework sequences which maintain their correct spatial orientation have the requisite antigen-binding function. The specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing antibodies comprising substitutions, additions or deletions within the CDRs of the heavy and light chain of the antibody 2.13.2 that bind IGF-1R. The specification provides no direction or guidance regarding how to produce the myriad of human antibodies, which contain a modified variable region as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. The scope of the claims must bear a reasonable correlation with the scope of enablement. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

In view of the teachings above and the lack of guidance, objective evidence, and or predictability in the specification, it would require undue experimentation by one of skill in the art to practice the claimed invention as broadly claimed.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 3-13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitsaides et al (XP-002293672; IDS-12/08/2004) in view of Cohen et al (WO 02/053596; International Publication Date:07/11/2002, IDS-12/08/2004) and Masferrer (PGPUB 20040127470; Claims Priority to 12/23/1998) and Carosella et al (PGPUB 20040209296, Claims Priority to 10/13/2000).

The applied reference, Chen et al, has a common inventor, with the instant application. Based upon the earlier effective U.S. filing date of the reference, it

constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 1, 3-13 and 16 are a method of treating a disorder in a mammal comprising administering to said mammal an effective amount of a human anti-IGF-IR antibody wherein the disorder is multiple myeloma, wherein the antibody comprises the CDRs of the antibody 2.13.2, wherein the antibody has a binding affinity for human IGF-1R of K_d of 8×10^{-9} or less and inhibits the binding between human IGF-1R and IGF-1 with an IC_{50} of less than 100nM, wherein the heavy and light chain amino acid sequences are obtained from human genes DP-47 and A30, respectively. The claims further comprise administering antibodies in combination with analgesic agent such as ibuprofen, anti-emetic agent such as granisetron hydrochloride, anti-vascular agent

such as bevacizumab and anti-proliferative agent such as PDGFR inhibitors and autologous tumor vaccines.

Mitsaides et al teach that IGF/IGF-1R system is a major therapeutic target for Multiple Myeloma (MM), and that anti-IGF-1R antibody suppressed the growth of MM patient tumor cells. Mitsaides et al teach that IGF-1R plays a major role in growth/survival of a wide range of neoplasms, including MM, and that blockage of IGF-1R with anti-IGF-1R antibodies can be clinically applicable for patients with MM. Mitsaides et al does not teach method of administering the anti-IGF-1R antibody 2.13.2, the human genes and the combination with various therapeutic agents. These deficiencies are made up for by Cohen et al, Masferrer and Carosella et al.

Cohen et al teach anti-IGF-1R antibody 2.13.2, and a method of treating cancer in a human comprising the step of administering to the human an amount of said antibody effective to treat cancer (claims 24-26, page 94 in particular). Further Cohen et al teach that the antibody 2.13.2 has a binding affinity for human IGF-1R of K_d of 8 X 10^{-9} or less and inhibits the binding between human IGF-1R and IGF-1 with an IC_{50} of less than 100nM (claims 3 and 7, in particular). Cohen et al also teach obtaining the heavy chain amino acid sequence from human gene DP-47 and the light chain amino acid sequence obtained from human gene A30 (claims 8 and 10, in particular).

Masferrer teach (summary of the invention, in particular) pharmaceutical compositions comprising antibodies and analgesic agent such as ibuprofen, anti-emetic

agent such as granisetron hydrochloride, anti-vascular agent such as bevacizumab and anti-proliferative agent such as PDGFR inhibitors, for treating cancers.

Carosella et al teach administering antibodies in combination with autologous tumor vaccines to treat tumors (claims 14, 20 and 22, in particular).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to produced a method of treating multiple myeloma in a mammal comprising administering a human anti-IGF-IR antibody, 2.13.2, wherein the antibody has a binding affinity for human IGF-1R of K_d of 8 X 10^{-9} or less and inhibits the binding between human IGF-1R and IGF-1 with an IC_{50} of less than 100nM, wherein the heavy and light chain amino acid sequences are obtained from human genes DP-47 and A30, respectively in combination with variety of agents as instantly claimed.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have produced a method of treating multiple myeloma in a mammal comprising administering a human anti-IGF-IR antibody, 2.13.2, wherein the antibody has a binding affinity for human IGF-1R of K_d of 8 X 10^{-9} or less and inhibits the binding between human IGF-1R and IGF-1 with an IC_{50} of less than 100nM, wherein the heavy and light chain amino acid sequences are obtained from human genes DP-47 and A30, respectively in combination with variety of agents as instantly claimed in view of Mitsaides et al, Cohen et al, Masferrer and Carosella et al

because Mitsaides et al teach that anti-IGF-1R antibody suppressed the growth of MM patient tumor cells and that blockage of IGF-1R with anti-IGF-1R antibodies can be clinically applicable for patients with MM, and because Cohen et al teach a method of treating cancer in a human comprising the step of administering to the human an anti-IGF-1R antibody 2.13.2, wherein the antibody has a binding affinity for human IGF-1R of K_d of 8 X 10^{-9} or less and inhibits the binding between human IGF-1R and IGF-1 with an IC_{50} of less than 100nM, in addition to teaching obtaining the heavy and light chain amino acid sequences are obtained from human genes DP-47 and A30, and because Masferrer teach pharmaceutical compositions comprising antibodies and analgesic agent such as ibuprofen, anti-emetic agent such as granisetron hydrochloride, anti-vascular agent such as bevacizumab and anti-proliferative agent such as PDGFR inhibitors, and becuase Carosella et al teach administering antibodies in combination with autologous tumor vaccines to treat tumors.

Thus, since the art recognizes that IGF/IGF-1R system is a major therapeutic target for Multiple Myeloma (MM), and that antibody 2.13.2 is useful in treating IGF-1R associated cancers, one of ordinary skill in the art would be motivated and would have a reasonable expectation of success, in the interest of developing a successful therapeutic strategy for multiple myeloma patients, to utilize the anti-IGF-1R antibody, 2.13.2, as taught by Cohen et al to treat multiple myeloma because Mitsaides et al teach that blockage of IGF-1R with anti-IGF-1R antibodies can be clinically applicable for patients with MM, including the various agents as claimed because Masferrer and

Carosella et al teach treating cancers comprising administering antibodies in combination with various agents.

Therefore, it would have been obvious to one of ordinary skill in the art and one would have been motivated at the time of the invention to specifically utilize the anti-IGF-1R antibody, 2.13.2, in combination with various agents as claimed to treat multiple myeloma, since it has been held to be within general skill of a worker in the art to select a known concept, such as the important role of IGF-1R in growth/survival of multiple myeloma and therapeutic advantage of anti-IGF-1R antibodies for Multiple Myeloma patients, and combine with the known material, such as anti-IGF-1R antibody 2.13.2, on the basis of its suitability, which is treating IGF-1R associated cancers, for the intended use as a matter of obvious design choice. *In re Leshin*, 125 USPQ 146. Because the claimed antibody 2.13.2 is known to treat IGF-1R associated cancers in the prior art and anti-IGF-1R antibodies are taught to be clinically advantageous for treating Multiple Myeloma patients, the development of a method to treat multiple myeloma comprising administering anti-IGF-1R antibody, 2.13.2, does not present a novel feature of the claimed invention. Since, one of ordinary skill in the art at the time of the invention would recognize that anti-IGF-1R antibody, 2.13.2, of Cohen et al, can be applied for therapeutic strategy of treating multiple myeloma with anti-IGF-1R antibodies of Mitsaides et al, it would have been obvious to produce a method of treating multiple myeloma comprising administering anti-IGF-1R antibody, 2.13.2.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

13. Claims 1, 3-8 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitsaides et al (XP-002293672; IDS-12/08/2004) in view of Emanuel et al (PGPUB 20020151508, Claims Priority to 02/09/2001) and Masferrer (PGPUB 20040127470; Claims Priority to 12/23/1998) and Carosella et al (PGPUB 20040209296, Claims Priority to 10/13/2000).

Claims 1, 3-8 and 16 have been described supra.

Mitsaides et al has been described supra. Mitsaides et al does not teach method of administering to the anti-IGF-1R antibody to a patient and the combination with various therapeutic agents. These deficiencies are made up for by Emanuel et al, Masferrer and Carosella et al.

Emanuel et al teach (detailed description of the invention, in particular) methods for treating cancers comprising administering a therapeutically effective amount of an antibody directed against the growth factor receptor associated with the cancer.

Masferrer has been described supra.

Carosella et al has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to produced a method of treating multiple myeloma in a mammal comprising administering a human anti-IGF-IR antibody in combination with variety of agents as instantly claimed.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have produced a method of treating multiple myeloma in a mammal comprising administering a human anti-IGF-IR antibody in combination with variety of agents as instantly claimed a in view of Mitsaides et al, Emanuel et al, Masferrer and Carosella et al because Mitsaides et al teach that anti-IGF-1R antibody suppressed the growth of MM patient tumor cells and that blockage of IGF-1R with anti-IGF-1R antibodies can be clinically applicable for patients with MM, and because Emanuel et al teach (detailed description of the invention, in particular) methods for treating cancers comprising administering a therapeutically effective amount of an antibody directed against the growth factor receptor associated with the cancer, and because Masferrer teach pharmaceutical compositions comprising antibodies and analgesic agent such as ibuprofen, anti-emetic agent such as granisetron hydrochloride, anti-vascular agent such as bevacizumab and anti-proliferative agent such as PDGFR inhibitors, and becuase Carosella et al teach administering antibodies in combination with autologous tumor vaccines to treat tumors.

Thus, since the art recognizes that IGF/IGF-1R system is a major therapeutic target for Multiple Myeloma (MM), and that antibodies directed towards growth factor receptors associated towards cancers can be used to treat cancers, one of ordinary skill in the art would be motivated and would have a reasonable expectation of success, in the interest of developing a successful therapeutic strategy for multiple myeloma patients, to develop a method of administering anti-IGF-1R antibody to multiple myeloma patients because Mitsaides et al teach that blockage of IGF-1R with anti-IGF-

1R antibodies can be clinically applicable for patients with multiple myeloma, including the various agents as claimed because Masferrer and Carosella et al teach treating cancers comprising administering antibodies in combination with various agents.

Therefore, it would have been obvious to one of ordinary skill in the art and one would have been motivated at the time of the invention to specifically utilize the anti-IGF-1R antibody in combination with various agents as claimed to treat multiple myeloma, since it has been held to be within general skill of a worker in the art to select a known concept, such as the important role of IGF-1R in growth/survival of multiple myeloma and clinical advantage of anti-IGF-1R antibodies for Multiple Myeloma patients, and combine with the known material, such as treating cancers comprising administering a therapeutically effective amount of an antibody directed against the growth factor receptor associated with the cancer, for the intended use as a matter of obvious design choice. *In re Leshin*, 125 USPQ 146. Because anti-IGF-1R antibodies are taught to be clinically advantageous for treating Multiple Myeloma patients, the development of a method to treat multiple myeloma comprising administering anti-IGF-1R antibody, does not present a novel feature of the claimed invention. Since, one of ordinary skill in the art at the time of the invention would recognize that anti-IGF-1R antibody can be applied for therapeutic strategy in treating multiple myeloma because it was well known in the art to treat cancers comprising administering antibodies directed towards the growth factor receptors associated with cancers, it would have been obvious to produce a method of treating multiple myeloma comprising administering anti-IGF-1R antibody.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

14. No claims are allowed

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Respectfully,
Parithosh K. Tungaturthi
Ph: (571) 272-8789

/David J Blanchard/
Primary Examiner, Art Unit 1643